

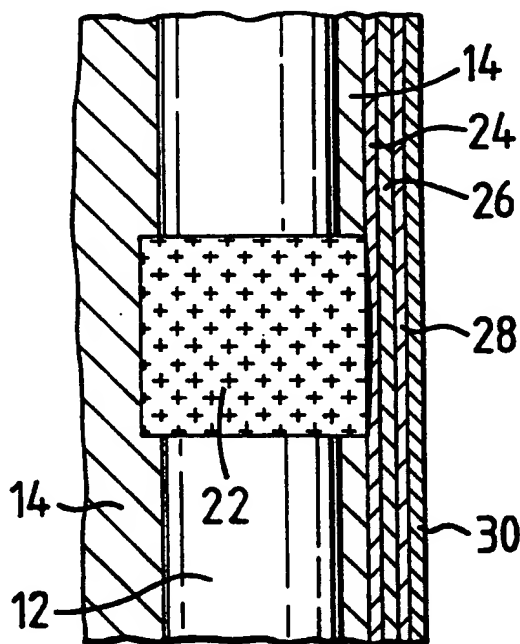


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<b>(21) International Application Number:</b> PCT/EP93/02772 <b>(22) International Filing Date:</b> 7 October 1993 (07.10.93)  <b>(30) Priority data:</b> 965,193                      23 October 1992 (23.10.92)      US  <b>(71) Applicants:</b> OPTEX BIOMEDICAL, INC. [US/US]; 2202 Timberloch Place, Suite 220, The Woodlands, TX 77380 (US). LUCAS, Brian, Ronald [GB/GB]; 135 Westhall Road, Warlingham, Surrey CR6 9HJ (GB). <b>(72) Inventor:</b> SINGH, Raghuvir ; 109 E. Wavy Oak, The Woodlands, TX 77381 (US). <b>(74) Common Representative:</b> LUCAS, Brian, Ronald; Lucas & Co., 135 Westhall Road, Warlingham, Surrey CR6 9HJ (GB).		<b>(81) Designated States:</b> CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>

**(54) Title:** FIBRE-OPTIC PROBE FOR THE MEASUREMENT OF FLUID PARAMETERS**(57) Abstract**

An optical probe for colorimetric measurement is provided which includes a body (14) having a tip and one or more sensors. Each sensor is defined by an optical fibre (12) in the body having a small slice extracted from it at a point along its length at a location adjacent to the tip so as to form an optical gap, at least one chamber opening to the surface of the body and extending into the interior of the body so as to expose the faces of the optical fibre at the optical gap, colorimetric sensor material in the chamber, and analyte-permeable membrane means applied to the body so as to cover the opening to the chamber. The colorimetric sensor material comprises a water soluble indicator covalently bonded to solid support material or over-coated or encapsulated with a water-insoluble coating or fluid. The sensors may be for pH, pCO<sub>2</sub> and pO<sub>2</sub>. An oxygen sensor material based on Ru (1,10-phenanthroline) chloride is applied as a paste made by mixing a dyed lichrosphere powder with an uncured elastomer. Methods for preparing a pH sensor material and a carbon dioxide sensor material involve hydroxyethyl cellulose. A permeable membrane derived from cellulose acetate, an anti-thrombogenic coating (30) and calibration solutions are also described.



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FIBRE-OPTIC PROBE FOR THE MEASUREMENT OF FLUID PARAMETERS

This invention relates to optical sensors and to materials and methods for making optical sensors. In one aspect, the invention is directed to multiple fibre  
5 optical sensor probes for sensing and/or monitoring fluid parameters, including but not limited to physiological blood characteristics such as blood pH and gas concentrations. In another aspect, it is concerned with the provision and use in a single catheter-like  
10 probe of a plurality or multiplicity of sensors. The invention is further concerned with materials for and methods for making fibre-optic probes useful for measuring and monitoring blood gases, pH, and fluid electrolytes.

15 Physiological measurement of blood gases and hydrogen ion concentration (pH) is important for a variety of medical reasons. Myocardial contractility after cardiac surgery is strongly influenced by the acid-base balance of the patient's blood. Patients with  
20 low cardiac output or with severe pulmonary disease show strong signs of acid-base imbalance accompanied by changes in the peripheral circulation or in ventilation-perfusion relationships. Further, the optical determination or monitoring of blood oxygen or  
25 carbon dioxide levels during certain medical procedures, such as critical cardiopulmonary and cardiovascular by-pass heart surgery has numerous advantages. Equally important is the physiological measurement of pH in blood serum along with oxygen for haemoglobin  
30 dissociation cycle and other diseases e.g. sickle cell anaemia and malfunctions.

Fibre optic devices for measurement of blood gases, pH, electrolytes and glucose are well known. Certain prior art sensors usually include an indicator molecule  
35 (dye) such as a fluorescent or absorption dye which

fl. or  
ab. dye

interacts with the component to be sensed or measured. Typically an indicator, often in combination with an analyte permeable matrix, provides a sensing element or sensor means and is placed on or adjacent to a surface  
5 in the light path of the fibres. The interaction between the indicators and the component to be measured or sensed is monitored utilising signals carried by the fibres. Such a probe can be introduced into an artery to measure, depending on the type of dye molecule, various  
10 blood parameters such as pH, pCO<sub>2</sub> and pO<sub>2</sub>. US Patents No 4,682,895; 5,006,314; 4,974,929; 4,824,789 and European specification No. EP-A-0 352 610 describe various prior art probes.

*P/A  
probes*

15 It is a major aim of sensor/probe development to combine more than one sensor in a single probe so that a patient is not overtaxed with various probes introduced into his or her arteries. Such a combination or multiple sensor probe may, for example, contain pH, pO<sub>2</sub>, pCO<sub>2</sub>, and/or a stabilised element such as a thermocouple wire.

20 The present invention, in one embodiment, discloses an implantable blood gas sensor device and methods and materials for making optical probes with one or more sensors, including, but not limited to, multiple sensor probes for measuring blood gases and pH.

25 This invention provides, in one embodiment, a drift-free fibre-optic sensor suitable for monitoring and preferably for continuously monitoring intra-arterial physiological blood gases and other analytes. One or more analyte permeable matrices or  
30 membranes encapsulate an indicator matrix inside a chamber (cell or cavity) situated in the path of light from an optical fibre (see e.g. US Patent No 5,124,139, the disclosure of which is incorporated herein by reference and a US Patent Application entitled "Optical  
35 Sensor For Fluid Parameters", filed in 23rd October 1992

*inc. by  
ref.*

and given the serial number 08/....., the disclosure of which is also incorporated herein by reference). The indicator matrix contains a dye (indicator molecule) adsorbed or immobilised on a selected solid surface support or covalently bonded or linked to a selected solid support which may be a polymer support, preferably a controlled pore glass e.g. aminoargyl CPG, average size 5  $\mu$ m particles commercially available from CPG Inc., or covalently linked to a controlled pore glass by methods described in the prior art. In a further type of analyte sensor, the support may be a silica gel based highly porous material e.g. Lichrosphere particles (keiselgur/silica gel) of uniform size (preferably about 10 micrometer) or Kieselgel (chromatography grade) or Chromosorb (Rohm Haas), or it may be a polymer e.g. XAD-4, Dow Sorb (The Dow Chemical Company) or another polymer which is related to or a derivative of PMMA. Loading or filling of an indicator matrix is done using a slurry, paste or cement-like dough made with a support polymer which is preferred or with a non-ionic gel e.g. hydroxyethyl cellulose, hydroxymethylpropyl cellulose (HMPC), Methocel (Dow Chemical Company), Ethocel (Dow Chemical Company), Kollidones (BASF, Inc), Dextran, polyvinyl pyrrolidone (PVP), a polyethylene glycol, a silicone fluid e.g. a polydimethyl siloxane or a derivative thereof. A drift-inhibited or a drift-free performance can be obtained with such a sensor probe having indicator molecules encapsulated within analyte permeable membranes of considerably less than about 20-30  $\mu$ m thickness.

The gas or analyte permeable membranes, coatings or layers which can be used to produce sensors having a fast response and specific selectivity when presented with a target or unknown analyte are carefully made preparations utilising polymers such as cellulose

acetate, cellulose acetate esters, siloxanes, polycarbonate copolymers, polyurethanes, ethyl vinyl acetate copolymer, silicones and PVC which are carefully cast or filmed from polar or nonpolar organic solvents.

5 The porosity, gas permeability and flexibility of such membranes or films can be adjusted by the addition of minor amounts of components such as water, methanol, zinc salts, magnesium salts or mixed solvents.

Certain preferred probes or sensors according to  
10 the invention have an opaque or light-protecting cover, coating or overcoat. The overcoat provides durability and mechanical strength and inhibits or prevents peeling or falling apart of the membrane when inside a conduit e.g. a human artery during a cardiovascular procedure  
15 when the probe or sensor is being used to monitor blood gases or other blood analytes. The overcoatings preferably are permeable to the component or components being sensed by more than one sensing indicator in the probe and should be sufficiently permeable to an analyte  
20 to be measured or determined that they can selectively allow the sensing molecule to detect analyte change. The opaque coating can be distributed to cover all the analyte chambers, cells or areas sensitive to indicator molecules. Such opaque coatings may also prevent outside  
25 light from entering into an indicator chamber, reduce migration of molecules from the chamber, act as a reflector for internal light (e.g. signals in an optical fibre) and impart strength and a uniform physical appearance to the probe.

30 In certain embodiments of the invention, sensors may be made using solvent-based film or dip coating by a semi-automatic process in which an analyte-sensitive indicator or dye molecule becomes covalently bonded to or adsorbed/admixed in a support matrix formulation.  
35 This method can facilitate mass production of the

*Substrate* probes. The coatings or membranes can be applied by dipping, spraying or painting the relevant area of a probe surface.

Solvents used in the production of the membranes or coatings are preferably selected so that the polymer material or its precursors are completely soluble. Such solvents are preferably non-aqueous and may be polar or non-polar organic solvents. Suitable solvents include hydrocarbon solvents, chlorinated hydrocarbon solvents, and alcohol, ether and ketone solvents. Methylene chloride, ethylene chloride, acetone and methanol are particularly useful.

The biocompatibility of implantable sensors is a prime consideration in the clinical acceptance of sensor probes and from the standpoint of patient safety they should not give rise to infection or damage to blood vessels. Sensor probes for in vivo use therefore preferably incorporate biologically compatible materials e.g. silicone, siloxane or urethane coatings and/or materials which satisfy or preferably exceed minimum biocompatibility standards.

The thicknesses of the membranes or coatings may be an important factor providing reliable and quantitative permeability and response time. The thickness parameters over the probe sensor body may vary uniformly within a range of 10-20  $\mu\text{m}$  and most preferably 12-15  $\mu\text{m}$ .

*t* In a preferred form of the invention, a multi-sensor probe has an applied overcoating which inhibits formation or build-up of blood clots during clinical procedures in which the probe is within a human artery and in contact with blood. Examples of anti-thrombogenic reagents include commercially available heparin-benzalkonium salt complex (H-BAC), tridodecylammonium salt complex (TDMAC) of heparin, steara-alkonium salt complex of heparin and films made

of cellulose derivatives with long alkyl chains. Films of these reagents are cast from mainly polar solvents e.g. alcohols except in those cases where a combination of solvents is needed to dissolve the reagent.

5        It is preferred that a sensor or probe according to the invention should undergo individual sterilisation inside a pouch, package or sterile container e.g. a plastics or foil pouch bag, typically accompanied by instructions for use. Sterility of the probe or sensor  
10 may be brought about by known methods e.g. irradiation with gamma-rays or an electron beam or chemical sterilisation. Gamma ray sterilisation is preferred because chemical sterilisation with e.g. ethylene oxide can give rise to objectionable residues and electron  
15 beam sterilisation may be incomplete. Sensor probes can be packed in a fully hydrated condition, especially soaked in an optical validation solution (OVS) or a calibration fluid.

      A sterilised sensor probe can easily be calibrated  
20 by placing the probe in an optical validation solution (OVS). and allowing it to equilibrate. After equilibrium has been reached gases are bubbled through the solution to adjust it to two different pH values and to bring the OVS to known concentrations of CO<sub>2</sub> and O<sub>2</sub> comparable to  
25 the concentrations that exist in blood to permit calibration of the probe for each parameter. At this stage the probe is preferably independently tested for CO<sub>2</sub> response in order to ensure that it is functioning as a CO<sub>2</sub> sensor and not giving a misleading response to  
30 pH instead.

      The invention is further defined in the accompanying claims to which attention is directed.



An embodiment of the invention will now be further described with reference to the accompanying drawings, in which:

Figure 1 is a schematic view of a probe showing  
5 optical fibres, potting material, sensor chambers, a thermocouple wire, a polyimide sheath and a mark;

Figure 2 is an enlarged view in axial section of a part of the probe adjacent to a sensor chamber; and

Figure 3 is an enlarged perspective view of the tip  
10 of the probe showing the internal components and in particular a bundle of optical fibres and an optical chamber within the potting material.

Certain preferred embodiments of the optical probe sensor of the invention permit measurement of  
15 physiological blood gases ( $p\text{CO}_2$ ,  $p\text{O}_2$ ) and pH, but such probes can also be used to measure other physiological data such as electrolyte and glucose concentration which exhibit similar behaviour.

US Patent No. 5,124,130 describes the making of an  
20 optical probe with plastics fibres using a "bend" design, generally as shown in Figure 1. The fibre-optic sensor probe 10, according to the present invention, has optical fibres 12 in a body 14 of potting material, and has gaps or chambers 16a-16c formed in the optical  
25 fibres 12, which chambers can be filled with a desired chemical indicator. These indicators may be covalently bound to a solid support and matrix via chemical reaction and/or immobilised on polymers of choice or on an inert support such as controlled pore glass (CPG) or  
30 silica gel. These indicators can also be adsorbed on solid polymer supports. The indicator molecules can be held in place within the optical chambers in the form of a gel or paste slurry made with soluble polymeric compounds or insoluble polymer fluids such as silicone  
35 or siloxanes and their derivatives. The selectively

permeable membranes are used to encapsulate the indicator or cover the indicator inside the optical chambers to prevent loss of indicator compound and contamination thereof by undesired chemical species in the environment. A second membrane or overcoating which is usually light-opaque is applied over the permeable membrane to prevent escape of light, reflection of light within the chamber and cross-contamination by external light which on entry to the chamber could give a false signal. Finally an anti-thrombogenic or anti-clotting coating is applied over the entire surface of the probe body. The use of such coatings provides additional strength to the sensor probe during clinical procedures, prevents clot formation and prevents deposition of foreign materials such as blood proteins on the surface of the probe. After all the materials and especially the membranes have been properly cured, the fibre-optic probe can be stored in a hydrated condition for future use. The hydration may be provided by immersing the probe in calibration fluid within a container.

The choice of materials to be used in making the fibre-optic sensor probe (Fig. 1) is greatly influenced by the need to satisfy simultaneously many requirements. Most importantly, the indicator support matrix (Fig. 2) should bond or immobilise the indicator dye molecules effectively and not permit them to leach out over the period of time of the assay. Signal drift can result from leakage or creeping of indicator molecules, especially water-soluble molecules like phenol red and similar acid-base indicators and soluble luminescent dye molecules. Preferably water-soluble indicators are covalently bonded to a component or solid support matrix, or a dyed support is overcoated or encapsulated with a water insoluble coating or fluid e.g. a silicone. A sensor probe made in this way has reduced drift or is

drift-free, and there is little or no detectable leakage or diffusion of indicator molecules from the matrix (Fig. 2) in the environment of use over the time period of the assay or measurement.

5 Referring to Fig. 2, the indicator matrix or support preferably permits the free passage in or out of the analyte substance or component, i.e. the support should be analyte permeable. For physiological measurements where the analyte is dissolved or dispersed  
10 in an aqueous solution, the support for the indicator is preferably hydrophilic as well as porous to the analyte component (e.g. hydrogen ions or carbon dioxide). Where the analyte is oxygen, the support matrix is preferably highly permeable to oxygen gas and allows the analyte to  
15 come into full contact with the indicator molecules. However, it is important to select the support matrix from the standpoint of hydrophilicity to prevent undue swelling thereof. The pore size of the support matrix is preferably large enough to permit the passage of an  
20 analyte of interest but small enough to preclude passage of unwanted substances such as blood proteins which could physically or chemically interfere with the measurements.

The support matrix 22 is preferably optically clear  
25 and in order to minimise light scattering preferably has a refractive index that matches that of the optical fibre core and that of the potting material. In addition it is preferred that the support matrix should be of a material that does not shrink or crack upon drying or  
30 rehydration, and which retains its rigidity and strength during use in blood vessels.

In a preferred form of probe according to the invention, a first analyte indicator 16a is sensitive to pH, a second analyte indicator 16b is sensitive to  
35 carbon dioxide concentration, and a third analyte

Permeable  
matrix

porous  
matrix

indicator 16c is sensitive to oxygen concentration. The probe may also have a built-in thermocouple 18. Hydrophobic matrix material for a pH and pCO<sub>2</sub> sensor can be an ion permeable polymer material which is compatible with the other components of the system. Examples of such materials include hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), hydroxypropyl methyl cellulose (HPMC), Kollidones or Povidones, hydrogels, polyacrylamide, PVA and the like. Hydrophobic solid support materials include Lichrospheres, silica gels, fumed silica, XAD-4 (Amberlite from Rohm-Haas) and the like.

In embodiments in which the indicator molecule is water-soluble and adsorbed on a solid surface such as in an oxygen probe according to the invention, the solid support is preferably uniformly encapsulated in or coated with a water repellent polymer matrix to prevent leaching or loss of the indicator material due to gradual dissolving thereof. Such materials are preferably gas permeable and water insoluble, e.g. silicone fluids, dimethylsiloxanes and their derivatives, polymeric elastomers, room temperature vulcanising (RTV) silicones, silicone adhesives and sealants (UV cure and room temperature cure).

A dye which is suitable for use as the indicator material preferably has the following characteristics:

1. It should be capable of excitation by visible wavelengths which can be transmitted along plastics optical fibres of the type which do not break when subjected to sharp bending, are highly flexible and can be easily coupled to other fibres or devices.

2. It should give an optical response in the presence of the targeted analyte component when immobilised on the indicator solid support and converted into matrix paste.

The response of the indicator should be highly specific

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for the targeted analyte in order to minimise interference and background signal noise. To permit continuous monitoring it is preferred that the reaction between the indicator molecule and the analyte should be reversible.

3. It should be resistant to light and to aging.
4. It should be non-toxic.
5. In the case of an oxygen-sensitive dye, it should have sufficient oxygen quenching ability and a long mean lifetime of the excited state so as to permit  $pO_2$  measurements to be obtained to the nearest 1 mm Hg.
6. The pH range at which the dye is required to work is 6.7 to 7.8 and the dye should be an absorption based dye having a  $pK_a$  in or close to that range.
7. It should be stable to ordinary, UV and gamma radiation.

Many UV excited dyes have a high quenching sensitivity, but the requirement of visible light excitation is difficult to meet. An example of such a dye is pyrene dibutyrate. Other suitable dyes are reported in the references given herein. Metal complexes are considered to be the best indicators for a  $pO_2$  sensor, and the oxygen-sensitive fluorescent dye tris (1,10-phenanthroline)Ru(II) chloride (obtainable from Aldrich) is a particularly preferred dye, although other salts of this cation may also be used e.g. with anions such as other halides, thiocyanate, perchlorate, hexafluorophosphate and/or tetrafluoroborate. Other suitable oxygen-sensitive fluorescent dyes include salts of a cation of a transition metal such as ruthenium (II), osmium (II) and rhenium (III) complexed with a ligand such as 2,2'-bipyridine or a derivative thereof, 1,10 phenanthroline or a substituted derivative thereof. Example I gives protocols for making a  $pO_2$  indicator complex attached to a solid support and support matrix.

*CO<sub>2</sub>/pH  
abs. dyes*

5 In one preferred embodiment of the invention for pH and pCO<sub>2</sub> sensor probes, there may be used such absorption-based dyes as phenol red and bromothymol blue (both commercially available from Sigma Chemical Co.) and derivatives thereof.

10 It is preferred that the selectivity, specificity and reversibility of the response of the indicator to the analyte should not change after the indicator has been covalently bonded or immobilised on a polymer or other solid surface. It is also necessary that the indicator should not lose its analyte specific sites after immobilisation, and steric hindrance of those analyte specific sites is preferably minimised. The indicator molecule is therefore preferably uniformly  
15 bound to the solid support in a site-specific manner that preserves the optical response behaviour of the molecule to the analyte. For this purpose, aminoarylated controlled pore glass (C.P.G. Inc, 5 µm mean size) is preferred and may be used to covalently link the  
20 indicator molecule (phenol red or bromothymol blue). Other suitable absorption dyes such as chlorophenol red, bromocresol purple and nitrophenol can also be used. *Others* Alternatively, unmodified controlled pore glass (Pierce, CPG or Fluka) can be used to bond the indicator molecule  
25 by treating the glass with known functionalised groups such as γ-APTSi (3-aminopropyltriethoxy silane) and making it amino functional (Baldini et al). The free arylamino group is then reacted with the indicator molecule of choice, for example by diazotization and  
30 coupling with indicator molecules such as phenol red that have strong electron releasing groups. This method is illustrated in Example 2.

35 In a further form of the invention, the fluorescent dye molecule tris(1,10-phenanthroline) ruthenium(II) chloride can be adsorbed from solution onto a solid

support, for example Lichrospheres (10  $\mu\text{m}$  particles, E.M. Science). To provide a good gas-permeable water repellent barrier to indicator molecules adsorbed on the solid support, a silicone fluid is mixed with or smeared on the support to give a uniform paste or slurry. Examples of the fluids are polydimethylphenylsiloxane, a silicone elastomer e.g. Dow's MDX 4210, uncured polydimethylsiloxanes (high viscosity), RTV silicone or substituted siloxane, or preferably an uncured silicone elastomer e.g. Dow MDX 4210 (Part A) or silicone fluid e.g. Dow Corning 556, cosmetic grade. In order to make a pH or  $\text{pCO}_2$  sensor probe according to the invention, indicator molecules are covalently bound to a hydrophilic polymer e.g. hydroxyethyl cellulose, hydroxypropyl cellulose, Kollidone (PVP), cellulose, methocel and hydrogel. The preferred matrix is hydroxyethyl cellulose (Polysciences, Inc and Fluka) which provides a stable and uniform slurry containing the indicator molecules which facilitates loading of the indicator into a chamber.

A variety of polymers may be used for the body 12 of the sensor probe. For example, the polymer may be a polyurethane, a cellulose acetate ester, polycarbonate, polyvinylcarbonate, polyvinyl butyrate, silicone rubber or a polyphenylsilsesquioxane. In general most polymers may be used provided that they are easily soluble in solvents which do not attack the optical fibres used and cured potting materials may be used such as ELC 4481 (Electrolyte Corporation), DeSolute 3471-2-33 (DeSoto, Inc), FMD-8 (Loctite Corp.) and 186 M (Dymax Corp.).

In certain preferred embodiments of the invention a membrane as illustrated in Figure 2 is used to provide a gas-permeable solution or fluid impermeable envelope or membrane over the  $\text{pO}_2$  and  $\text{pCO}_2$  chambers to protect the indicator complex slurry within each chamber. In the

same embodiments the pH chamber may be enveloped or covered by a membrane which is selective and specific for hydrogen ions whilst impermeable to other substances such as proteins, and which also has the structure shown in Figure 2. In an alternative form of the probe, a second envelope or selective membrane is applied over the  $pCO_2$  and  $pO_2$  chamber area to ensure that these sensors are fully gas-permeable and water or solution impermeable, as illustrated in Figure 2. By applying an appropriate double membrane 24,26 e.g. of silicone and polyurethane over the  $pCO_2$  and  $pO_2$  indicators the serious problem can be solved of how to make the indicators sensitive to  $CO_2$  and  $O_2$  molecules but not sensitive to hydrogen ions. The present invention provides a full solution for this problem because the membranes 24,26 used are only permeable to gas molecules and not to hydrogen ions.

The determination of  $pCO_2$  can be carried out indirectly by measuring the change in pH of a colorimetric pH indicator (in this case phenol red) in the presence of a bicarbonate buffer medium in equilibrium with the local  $pCO_2$ . For maximum linearity the pH of the gel or slurry is adjusted to be equal to the dye  $pK_a$  (acid dissociation constant) at the midpoint of the range of  $pCO_2$  to be measured. The gel or slurry may therefore contain bicarbonate in a 35 millimolar concentration, which provides an effective range for a nominal  $pCO_2$  of 40 mm Hg, and it preferably also contains sufficient sodium chloride to make the medium isotonic. Successful operation of the  $pCO_2$  sensor probe also depends upon the stability of the bicarbonate buffered gel within the sample chamber. The use of gamma radiation to sterilise the probe can result in some degradation of bicarbonate with apparent loss of sodium bicarbonate. To avoid this, the bicarbonate buffer may



be mixed prior to use with an antioxidant reagent in a concentration of 0.1%. However, probes which are sterilised by other methods may not require the use of an antioxidant.

5 Preferred membrane materials include dimethyl siloxane bisphenol A carbonate copolymer (e.g. MEM 220 from Oxygen Enrichment Co), polyurethane (Tecoflex, solution grade SG80A from Thermedix), a cellulose acetate ester (e.g. 398-10 from Eastman Kodak), an  
10 ethylene-vinyl acetate copolymer (Scientific Polymer Products, Inc.) and polycarbonate (Aldrich Chemical Company). Solvent based film- or membrane-forming materials may be used and can facilitate mass production of the fibre-active sensor probes. The sensors may be  
15 simultaneously and uniformly coated as at 24 (Fig 2) by dipping, spraying or otherwise painting the probe body or indicator covering area. An opaque coating or membrane 28 which is gas and hydrogen ion permeable is made using opaque materials e.g.  $\text{TiO}_2$  powder  
20 (commercially available from Aldrich or Whittaker, Clarke and Daniels, Inc.), graphite powder (e.g. from the Asbury Graphite Mills, Aldrich and Johnson Matthey) and powdered carbon (Aldrich, Alfa and Lancaster Dispersion). The opaque overcoating 28 enhances the  
25 performance of the probe in several ways. It serves as a protective membrane over the sensors and isolates the optical indicator from the environment which is being measured or sensed. The sensor 16a, b or c is also  
30 isolated from external light including light from a second sensor located adjacent to the first sensor. Additionally, overcoatings in general can provide a suitable surface on which additional material can be located, for example a film or coating 30 of an anti-thrombogenic reagent.

35 The opaque coating or membrane 30 may be applied

over the whole surface area over an indicator, partly covered area, or simply covering the area adjacent the or each sensor chamber where the coating only protects the indicator complex or molecules. One such coating is  
5 based on cellulose acetate material modified for its porosity and strength. These coatings are water insoluble and mechanically strong and smooth and provide a surface with good permeability. It is preferred that these coatings should be made from material which is  
10 biocompatible and which does not lack compatibility with body fluids such as blood. Such coatings are stable, strong, biocompatible and do not leach away during the course of an assay.

The sensor probes must be sterile so that they can  
15 safely be introduced into the body. A preferred method of sterilising them is by means of gamma-radiation at a dose of typically 2.5 mrad. Gamma sterilisation is preferred because it avoids the risk of residual ethylene oxide being present in an alternative  
20 sterilisation method in which ethylene oxide is used and because of the hydrated nature of the sensor. Sensor probes are preferably packaged in hydrated condition for easy handling during gamma sterilisation and calibration. The sensor probes are preferably also  
25 packed individually in suitable containers such as foil pouches, typically accompanied by printed instructions for their use.

One form of multiple sensor according to the invention is stored pre-packaged in a container filled  
30 or saturated with OVS (optical validation solution). The system preferably incorporates one prepacked container containing calibration solution (OVS) having known values for each of the parameters to be measured at two different gas levels which may be defined by bubbling  
35 first and second gases through the solution to allow the

sensor to be calibrated on a two point basis. For example the first gas could contain 8% CO<sub>2</sub>, 3% O<sub>2</sub> and the balance nitrogen and the second gas could contain 3% carbon dioxide, 25% oxygen and the balance nitrogen. For reference purposes there may also be present a second container with a second optical calibration solution. Each container preferably contains a sufficient quantity of its solution to allow the sensor to be calibrated several times before it is inserted into the human body.

5 Calibration of a multiple sensor probe may be carried out by placing the probe in OVS, allowing it to equilibrate with the first gas by bubbling that gas through the solution and recording the blood gas data and pH by means of a blood gas analyser, and then

10 equilibrating the probe in the same solution with the second gas which is bubbled through the solution, after which the same data is recorded. Normal blood gas concentrations may be measured after the probe has been calibrated with OVS.

15

20 The optical validation solution(s) used herein should be stable homogeneous solutions that permit measurement of parameters such as pH, pCO<sub>2</sub> and pO<sub>2</sub> that it is subsequently desired to measure in vivo. One form of OVS comprises an aqueous solution buffered to a pH of

25 6.8 to 7.8 and containing sufficient bicarbonate ions to provide a pCO<sub>2</sub> of 15-90 mm Hg and a pO<sub>2</sub> of about 20-300 mm Hg after subsequent equilibration with gas mixtures of the desired composition. This solution may be used as a control for blood gas measurements. In order to

30 provide the desired pH for the respective normal acidosis and alkosis condition, a buffered material may be selected which has a pKa close to the working range of pH. Useful buffer materials for imparting the required pH to the calibration solution are:

## TES

(N-tris-(hydroxymethyl)methyl-2-aminoethanesulfonic acid), pKa 7.16 at 37°C;

## TRICINE

5 (N-tris-(hydroxymethyl)methylglycine), pKa 7.79 at 37°C;

## MOPS

(3-(N-morpholino)-propanesulfonic acid), pKa 7.01 at 37°C;

## HEPES

10 (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid), pKa 7.31 at 37°C.

These and other such buffers, including their sodium salts are described by Good et al, Biochemistry, Vol. 5 (1966) and Ferguson et al, Analytical  
15 Biochemistry, Vol. 104 (1980).

To increase the shelf life of the OVS and to inhibit bacterial or fungal growth, a preservative may be added during preparation of the solution. Useful antibacterial and fungicidal materials include ProClin  
20 300 (Rohm & Haas) which is preferred, sodium azide, benzyl alcohol, Kathon (Rohm & Haas) and mercury salts. The OVS solution may be packaged in a container and sealed into a foil pouch bag, in which case the occurrence of outgassing from the liquid to form gas  
25 bubbles within the container is significantly reduced or eliminated. The OVS solution can exhibit excellent stability and long shelf life.

Table 1 specifies an OVS which is effectively a blood facsimile. Its parameters are as indicated in  
30 Table 2.

Table 1

	Compound	Conc.(mmol/l)	grams/litre
	1. NaCl	100	5.840
5	2. KCl	4	0.298
	3. NaHCO <sub>3</sub>	25	2.100
	4. MgCl <sub>2</sub> .6H <sub>2</sub> O	1	0.203
	5. Na <sub>2</sub> HPO <sub>4</sub>	1	0.141
	6. CaCl <sub>2</sub> .2H <sub>2</sub> O	2	0.294
10	7. TES	15	3.440
	8. NaOH	1N	4.0 ml.

Table 2

	mixture	Gas pH (units)	pCO <sub>2</sub> (mm Hg)	pO <sub>2</sub> (mm Hg)
		Gas #1	7.14-7.26	53-59
				35-55
20	Gas #2	7.50-7.62	20-26	165-195
	No gas	7.10-7.37	40-70	150-180

The pO<sub>2</sub> probe does not need to be hydrated prior to operation and therefore does not need to be packed in hydrated conditions. As a part of a multiple probe sensor, a three sensor probe is preferably kept hydrated.

The invention will be further described with reference to the following examples:

#### Example 1- Oxygen Indicator

0.246 g (3 mmol/l) of Ru(1,10-phenanthroline)<sub>3</sub>Cl<sub>2</sub> obtained from Aldrich Chemical Co. was dissolved in 100 ml of double distilled water. 1.0 g of Licrospheres (10

µm size, obtained from E.M. Science) was mixed with this solution, and the resulting mixture was stirred for 2-3 hours to give a dyed Licrosphere powder which was filtered and dried in an oven at 100°C. 0.1 g of the  
5 dyed material was uniformly mixed (smeared) with 0.255 g of uncured silicone elastomer (Dow MDX 4210 Part A) until a consistent uniform paste was obtained.

#### Example 2 - pH and CO<sub>2</sub> Indicator

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0.40 g of phenol red dye (cell culture grade obtained from Sigma Chemical Co) was dissolved in 40 ml of 2N HCl. 1.0 g of controlled pore glass (CPG Inc) was mixed with this cold solution and the resulting mixture  
15 was stirred for 10 minutes and then cooled to -2°C for 2 hours. 0.64 g of sodium nitrite (Sigma Chemical) was slowly added under vacuum. The resulting mixture was stirred for 10 minutes, cooled to -2°C and maintained at this temperature for 2-3 hours. The resulting indicator  
20 glass was recovered by filtration through a 3 µm polycarbonate filter and the solid was washed with slightly basic distilled water until the washings showed no colour as tested by a spectrophotometer. The filtered solid was dried in air and then in an oven for 12 hours  
25 at 60-70°C.

Preferred support media or matrices for indicator complexes for pH and pCO<sub>2</sub> probes (made prior to mixing with a solid indicator) include the following:

(a) pH support media: 0.2 g of hydroxyethyl  
30 cellulose obtained from Polysciences Inc. was dissolved in 20 ml of optical calibration solution in a vial. The contents were mixed until no undissolved material remained in the vial.

(b) pCO<sub>2</sub> support media: 0.2 g of hydroxyethyl  
35 cellulose obtained from Polysciences Inc. was dissolved

in a vial with 20 ml of 35 mmolar bicarbonate buffer obtained by dissolving 0.336 g of sodium bicarbonate (Sigma cell culture grade) and 0.24 g of sodium chloride (Sigma cell culture grade) in 100 ml of tissue culture grade water. The contents were mixed until no undissolved material remained in the vial.

(c) to obtain the pH indicator complex, 0.1 g of indicator dyed glass made as described in this Example was uniformly mixed with 0.4 g of pH support media.

(d) to obtain the pCO<sub>2</sub> indicator complex 0.1 g of indicator dyed glass made as described in this example was uniformly mixed with 0.4g of pCO<sub>2</sub> support media.

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## Example 3 - pH Membrane

0.80 g of magnesium perchlorate (GFS Chemicals) was dissolved in 15 ml of pure methanol (Sigma), after which  
5 20 ml of methylene chloride (Fisher) was added. 2.2 g of powdered cellulose acetate (Eastman Kodak, product 398-10) was dissolved slowly over a period of 6 hours in this mixture to give a clear homogeneous viscous solution.

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## Example 4 - Hydrophobic Gas-Permeable Patch Membrane Material

1.05 g of dimethyl siloxane bisphenol A polycarbonate copolymer resin (Oxygen Enrichment Co) was  
15 dissolved in 15 ml of ethylene chloride (protein sequencing grade from Sigma) to give a clear viscous solution.

20

## Example 5 - Gas Permeable Dip Membrane

0.72 g of polyurethane resin (Tecoflex SG 80A, Thermedix) was dissolved in 20 ml of methylene chloride (Fisher) to give a clear viscous solution:

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## Example 6 - Opaque Coating

0.15 g of magnesium perchlorate (GFS Chemicals) was dissolved in 12 ml of pure methanol (Sigma), after which  
30 19 ml of methylene chloride was added and 1.2 g of cellulose acetate (Eastman Kodak product 398-10) was dissolved in the resulting mixture over a period of 6 hours. After a uniform solution had been obtained, 2.4 g of graphite powder (Asbury Graphite Mills) was mixed  
35 into the solution and the whole contents were stirred



for 6 hours to complete dispersion and uniform mixing to give a black viscous material.

#### Example 7 - Opaque Coating

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Material to form a white overcoating membrane was made in a similar manner to the pH membrane material described in Example 3 except that 2.0 g of  $\text{TiO}_2$  powder (Aldrich Chemical Company) was added to the solution in a container, and the contents were mixed for 6 hours to uniformly mix and consistently disperse the powder, producing a white opaque mixture.

#### Example 8 - Anti-thrombogenic Coating

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40.0 ml of H-BAC (a heparin complex of benzalkonium chloride, Polysciences Inc. product No 18332) was slowly evaporated to near dryness in an oven at 70 °C. 30 ml of pure methanol was added to the resultant sticky mass, and the resulting mixture was stirred for 6-8 hours after which the residue had dissolved completely giving a clear mixture. Alternative coating materials include TDMAC-Heparin (Polysciences Inc., product No 03813), S-BAC-Heparin (Stearyldimethylbenzylammonium complex with heparin, obtained from Bently/ Baxter) and Hydrogels.

#### Example 9 - Coating Application Method

A thin layer of coating or membrane is applied to a sensor to cover its indicator complex chambers either by applying membrane material or by dipping the probe into a solution of the membrane material. After the coating has been applied, the solvent is allowed to evaporate. In some cases the coating is cured in a humid

environment for several hours. In order to verify the integrity and strength of the coating, it is independently tested for adhesion, mechanical stability, peel strength and functionality.

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#### Example 10 - Coating Application Method

In a multi-sensor probe having three chambers e.g., a pH, pCO<sub>2</sub> and pO<sub>2</sub> indicator complex chamber, one on each fibre, the indicator complexes of Examples 1 and 2 are used to fill or load the chambers. Next a thin film or patch of specific membrane or coating is applied on the area of each chamber. A hydrophobic gas-permeable membrane is then applied on the area of the pCO<sub>2</sub> and pO<sub>2</sub>, preferably by a dipping technique. In a next step, the sensor body or probe is dipped in a hydrophilic membrane-forming material to form a membrane which covers all three chambers. Preferably an anti-thrombogenic coating or membrane is applied to the surface of the sensor probe. After proper curing the probe is immersed in an OVS for storage, further handling or testing.

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CLAIMS

1. An optical probe for colorimetric measurement, including:
  - a body having a tip; and
  - 5 one or more sensors each defined by an optical fibre in the body having a small slice extracted from it at a point along its length at a location adjacent to the tip so as to form an optical gap, at least one chamber opening to the surface of the body and extending
  - 10 into the interior of the body so as to expose the faces of the optical fibre at the optical gap, colorimetric sensor material in the chamber, and analyte-permeable membrane means applied to the body so as to cover the opening to the chamber,
  - 15 wherein the colorimetric sensor material comprises a water-soluble indicator retained by being (a) covalently bonded to solid support material or (b) by the support being overcoated or encapsulated with a water-insoluble coating or fluid.
- 20 2. The probe of claim 1, wherein there is present a  $pO_2$  sensor and the indicator is an oxygen-sensitive fluorescent metal complex.
3. The probe of claim 2, wherein the indicator is a salt with a cation of ruthenium (II), osmium (II) and
- 25 rhenium (III) complexed with 2,2'-bipyridine or a derivative thereof, 1,10 phenanthroline or a substituted derivative thereof and an anion which is a halide, thiocyanate, perchlorate, hexafluorophosphate and/or tetrafluoroborate.
- 30 4. The probe of claim 3, wherein the salt is of the tris (1,10-phenanthroline)Ru(II) cation.
5. The probe of any of claims 2-4, wherein the support is encapsulated or coated uniformly with a water-repellent polymer to prevent gradual dissolution
- 35 of the fluorescent metal complex.

6. The probe of claim 5, wherein the water-repellent polymer is a silicone fluid, dimethylsiloxane or a derivative thereof, polymeric elastomer, room temperature vulcanising silicone, or UV- or room temperature curing silicone adhesive or sealant.
7. The probe of any of claims 2-6, wherein the support is a porous glass or a porous silica gel-based material.
8. The probe of claim 7, wherein the support comprises porous glass particles about 5µm in size.
9. The probe of any preceding claim, wherein there is present a pH sensor..
10. The probe of claim 9, wherein the pH sensor comprises a pH sensitive fluorescent dye covalently bound to glass, said glass being mixed with a hydrophilic polymer which may be hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, cellulose, methocel or a hydrogel.
11. The probe of any preceding claim, wherein there is present a pCO<sub>2</sub> sensor.
12. The probe of claim 11, wherein the indicator is an isotonic paste comprising a water-soluble fluorescent dye sensitive to CO<sub>2</sub> covalently bonded to a support, sodium bicarbonate in an amount such as to adjust the pH of the indicator to the dye pKa at the midpoint of the pCO<sub>2</sub> to be measured, and an antioxidant.
13. The probe of claim 12, wherein the support is of glass to which the dye is bonded, the glass being mixed with a hydrophilic polymer which may be hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, cellulose, methocel or a hydrogel.
14. The probe of any preceding claim wherein there are two sensors responsive to different analytes.
15. The probe of any of claims 1-13, wherein there are three sensors responsive to different analytes.
16. The probe of any preceding claim, wherein there is

present a pH sensor contained by a hydrogen ion-permeable membrane means which is of a cellulose acetate ester or ethylene vinyl acetate copolymer.

17. The probe of any preceding claim, wherein there is  
5 present a  $p\text{CO}_2$  or  $p\text{O}_2$  membrane of a hydrophobic gas-permeable material.
18. The probe of claim 17, wherein the membrane is of a dimethylsiloxane bisphenol A carbonate copolymer or a polyurethane.
- 10 19. The probe of any preceding claim, further comprising a second envelope or protective membrane providing a double membrane for a  $p\text{CO}_2$  and/or  $p\text{O}_2$  chamber thereof so that the  $p\text{CO}_2$  sensor is not subject to hydrogen ion interference.
- 15 20. The probe of any preceding claim, further comprising an opaque overcoating which is gas and hydrogen ion permeable.
21. The probe of any preceding claim wherein the overcoating is of graphite or  $\text{TiO}_2$  in a cellulose ester.
- 20 22. The probe of any preceding claim having on its surface an anti-thrombogenic coating.
23. The probe of any preceding claim, wherein the body is of a cured potting material.
24. The probe of any preceding claim, wherein the or  
25 each optical fibre is doubled and has a sharp  $180^\circ$  bend at the tip thereof.
25. The probe of any preceding claim, having an outer diameter small enough to permit the probe to be inserted into a hypodermic needle.
- 30 26. The probe of any preceding claim, having an outer diameter small enough to permit insertion into a blood vessel.
27. The probe of any preceding claim, having an outer anti-thrombogenic coating.
- 35 28. The probe of any preceding claim, which is

chemically sterilised.

29. The probe of any preceding claim which is radiation sterilised.

30. The probe of any preceding claim, which is in a  
5 hydrated state.

31. A gas analyte sensor of an optical fibre probe,  
said sensor comprising an indicator matrix for  
disposition in a cavity in the optical fibre of the  
probe, the indicator matrix containing indicator  
10 molecules on a support, an analyte-permeable membrane  
covering the indicator matrix, and the support  
comprising (a) porous glass particles of about 5µm in  
size or (b) a silica gel based porous material or (c)  
either porous glass particles or silica gel based porous  
15 material and a support polymer of non-ionic gel.

32. The sensor of claim 31, wherein the non-ionic gel  
is of hydroxyethyl cellulose, hydroxymethyl propyl  
cellulose, methocel, ethocel, dextran, polyvinyl  
pyrrolidone, a polyethylene glycol or a silicone.

33. A gas analyte sensor indicator matrix paste for  
installation in a cavity of an optical fibre of a fibre  
optic sensor probe, the paste comprising an indicator  
matrix containing indicator molecules on a support  
comprising either porous glass particles or a silica gel  
25 based porous material and a support polymer of non-ionic  
gel.

34. A gas analyte permeable membrane comprising at  
least one coating or layer of a cellulose acetate ester.

35. A fibre-optic probe comprising a probe body, a  
30 plurality of optical fibres in the probe body, each  
optical fibre having a gas analyte sensor therein, and  
an anti-thrombogenic overcoating on the probe body.

36. A gas analyte sensor for an optical fibre of a  
fibre optic probe, the sensor comprising an oxygen-  
35 sensitive fluorescent dye which is tris-(1,10-phenan-

throline) Ru(II) chloride.

37. A gas analyte sensor for an optical fibre of a fibre optic probe, the sensor comprising an oxygen-sensitive fluorescent dye which is a ruthenium or  
5 other transition metal complex salt.

38. The sensor of claim 36 or 37, wherein the salt is adsorbed on a solid support of lichrospheres.

39. A method for preparing an oxygen indicator for an oxygen analyte sensor for installation in a cavity of an  
10 optical fibre of an optical fibre probe, the method comprising dissolving an amount of Ru (1,10-phenanthroline) chloride in an amount of water to produce a solution, adding an amount of lichrospheres to the solution, stirring the resulting mixture and filtering  
15 it to produce a dyed lichrosphere powder, drying the powder, and forming a paste by mixing the dried powder with an uncured elastomer.

40. A method for preparing a pH indicator complex for installation in a cavity of an optical fibre of a fibre  
20 optic probe, the method comprising dissolving hydroxyethyl cellulose in a blood facsimile solution, and mixing the solution with glass dyed with a pH indicator.

41. A method of preparing a carbon dioxide indicator  
25 complex for installation in a cavity of an optical fibre of a fibre optic probe, the method comprising producing a first solution by dissolving an amount of sodium bicarbonate and an amount of sodium chloride in water, producing a second solution by dissolving an amount of  
30 hydroxyethyl cellulose in an amount of the first solution, and mixing the second solution with glass dyed with a carbon dioxide indicator.

42. A method for preparing material for a permeable membrane for an analyte pH sensor for installation in a  
35 cavity of an optical fibre of a fibre optic probe, the

method comprising producing a first solution by dissolving an amount of magnesium perchlorate in an amount of pure methanol, producing a second solution by adding an amount of methylene chloride to an amount of the first solution, and producing a viscous solution by adding an amount of cellulose acetate powder to the second solution so that it dissolves slowly therein.

43. A method for producing an anti-thrombogenic coating for a fibre optic sensor probe, the method comprising evaporating an amount of a benzalkonium chloride complex of heparin to near dryness to produce a sticky mass, mixing an amount of methanol with the sticky mass, and stirring the resulting mixture until it clears.

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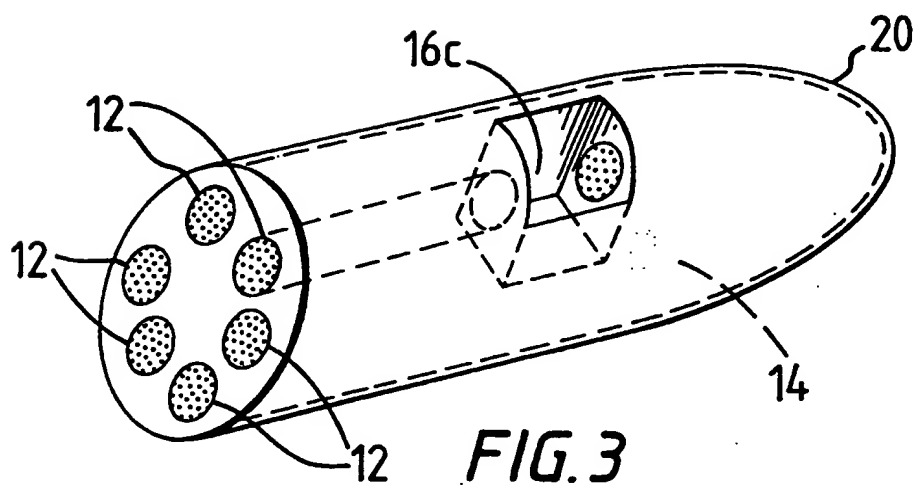
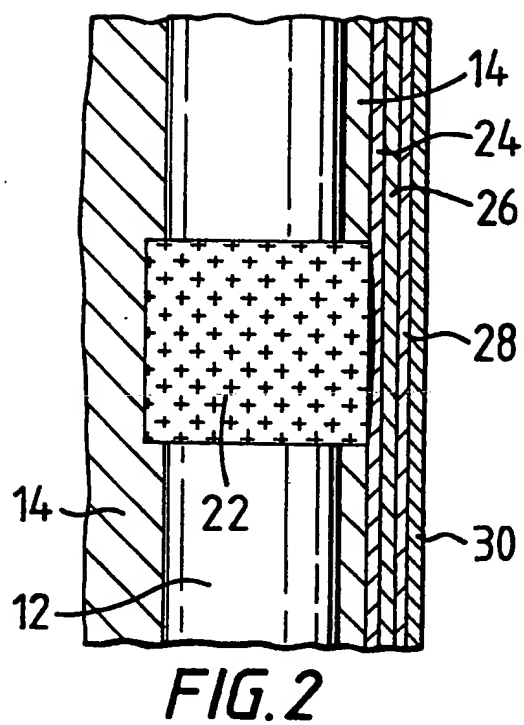
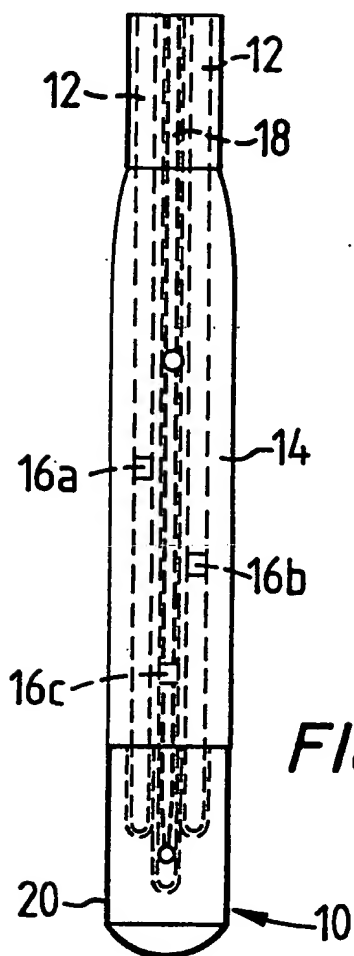
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## INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No

PCT/EP 93/02772

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 5 G01N21/64 G01N21/77 A61B5/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 5 G01N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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Y	US,A,4 727 730 (MEDEX) 1 March 1988	1,7-9, 11, 24-26,32
	see abstract see column 3, line 28 - line 66 see column 6, line 40 - line 57 see column 7, paragraph 1; figure 2 ---	31
Y	WO,A,87 00920 (OPTEX BIOMEDICAL) 12 February 1987 cited in the application see page 6, line 25 - line 28 see page 7, line 1 - line 4 see page 10, line 2 - line 7 see page 11, line 12 - page 12, line 5 see page 11, line 28 - line 35 see page 12, line 12 - page 13, line 9	1,7-9, 11,24-26
X	see figures 1,2 ---	31,33
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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Y	see example 3	32
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